RESEARCH NOTE

Mycobacterium tuberculosis at a comprehensive cancer centre: active disease in patients with underlying malignancy during 1990–2000

G. R. De La Rosa, K. L. Jacobson, K. V. Rolston, I. I. Raad, D. P. Kontoyiannis and A. Safdar

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

ABSTRACT

Thirty HIV-seronegative cancer patients with active tuberculosis were evaluated. Eighteen (60%) were immigrants, 19 (63%) had haematological malignancy, and fever was the most common presentation (97%). Of 19 (63%) patients with pulmonary tuberculosis, 11 (58%) were misdiagnosed initially as suffering from cancer following radiography. Death was attributed to tuberculosis for six (21%) of 29 patients who received anti-mycobacterial therapy. All four patients who had received high-dose systemic corticosteroids within 4 weeks of diagnosis of infection died, whereas two (8%) deaths occurred in 25 individuals without corticosteroid exposure ($p < 0.001$; OR 8.67). At this institution, active tuberculosis was rare, and was seen mostly in immigrants. Recent high-dose corticosteroid therapy is a significant predictor of mortality in cancer patients with tuberculosis.

Keywords Cancer, corticosteroids, *Mycobacterium tuberculosis*

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Mycobacterium tuberculosis is a serious infection worldwide; 8 million new cases and 3 million deaths/year have a substantial impact on global public health [1]. Compared with the general population, patients with adaptive cellular immune dysfunction are at increased risk of active tuberculosis [2]. Among oncology patients, those with Hodgkin's diseases and head and neck cancer have been considered to be at high risk of infection [3]. Patients undergoing allogeneic haematopoietic stem cell or organ transplantation in regions endemic for *M. tuberculosis* are also at increased risk [4]. However, the risk for transplant recipients in the USA and Europe remains low, although *M. tuberculosis* in immigrant populations in the USA remains an important health care concern [5,6].

During the last decade, urban outbreaks of isoniazid- and rifampicin-resistant *M. tuberculosis* strains have caused grave public health concern [7]. In contrast to patients infected with HIV, multidrug-resistant (MDR) tuberculosis is seldom observed in patients with cancer or following stem cell transplantation. The purpose of this study was to determine the characteristics of active tuberculosis in cancer patients during the 1990s.

All patients seen between 1 January 1990 and 30 June 2000 at the MD Anderson Cancer Center (Houston, TX, USA) with positive *M. tuberculosis* cultures were reviewed retrospectively. Patient and laboratory data were retrieved from the patients' charts and the hospital computer systems. Patients diagnosed with HIV, and a case reported previously [8], were excluded from the study. *M. tuberculosis* was isolated and identified by standard methods [9]. Antimicrobial susceptibility was determined according to National Committee for Clinical Laboratory Standards guidelines [10]. Disseminated tuberculosis was defined as infection involving two or more non-contiguous body sites, while neutropenia (granulocytopenia) was < 500 cells/mm^3, and lymphocytopenia was < 500 cells/mm^3. Significant corticosteroid use was defined as a cumulative dose of ≥ 15 mg/day of prednisone equivalent within the 4 weeks before diagnosis of infection. Protein–energy malnutrition was severe if the body mass index was < 16.0 kg/m^2. Death was attributed to *M. tuberculosis* in the absence of other terminal precipitating causes and with histological evidence of tuberculosis.

Thirty of 48 patients with active tuberculosis were included in the study. These 30 patients had a median age of 54 years (range, 23–88 years). During the 10 years of the study, the overall frequency

Corresponding author and reprint requests: A. Safdar, Department of Infectious Diseases, Infection Control, and Employee Health, 402, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA
E-mail: asafdar@mdanderson.org

Table 1. Characteristics of 30 patients with cancer and *Mycobacterium tuberculosis* infection

Patient characteristics	Number (%) of patients
Male:female	19:11
Immigrant	18 (60)
Neutropenia (cells/mm^3; absolute neutrophil count < 500)	6 (20)
Lymphocytopenia (< 500 cells/mm^3)	6 (20)
Systemic corticosteroids	4 (13)
Protein–energy malnutrition	6 (20)
Mild to moderate (BMI 18.4–16 kg/m^2)	3
Severe (BMI < 16.0 kg/m^2)	3
Underlying cancer	30 (100)
Haematological malignancy	19 (63)
Leukaemia[a]	10
Lymphoma[b]	6
Myelodysplastic syndrome	2
Multiple myeloma	1
Haematopoietic stem cell transplantation	4 (13)
Solid-organ malignancy	11 (37)
Head and neck cancer	4
Breast carcinoma	2
Urinary bladder cancer	2
Others[c]	3

BMI, body mass index.
[a]Leukaemia included chronic myelogenous leukaemia (n = 4), acute myelogenous leukaemia (n = 4), and acute (n = 1) and chronic (n = 1) lymphocytic leukaemia.
[b]Of six patients with lymphoma, five had non-Hodgkin's lymphoma and one had Hodgkin's disease.
[c]Others include one patient each with rectal cancer, cervical carcinoma and fibrosarcoma.

of active tuberculosis was 0.2/1000 new cancer diagnoses, and 1.3/1000 new leukaemia diagnoses. Patient characteristics are listed in Table 1. Of the 18 patients born in countries outside the USA, 11 (61%) were from Latin America.

Table 2. Characteristics of *Mycobacterium tuberculosis* infection in 30 patients with cancer

Infection characteristics	Number (%) of patients
Clinical presentation	
Fever	29 (97)
Anorexia	20 (67)
Cough	19 (63)
Dyspnoea	18 (60)
Weight loss	10 (33)
Haemoptysis	9 (30)
Night sweats	8 (27)
Site of infection	
Pulmonary[a]	19 (63)
Unilateral upper-lobe disease	14
Bilateral upper-lobe disease	2
Diffuse-nodular upper-lobe disease	1
Middle-lobe cavitary disease	1
Miliary disease pattern	1
Lymphadenitis	4 (13)
Pleurisy	3 (10)
Meningitis	1 (3)
Psoas abscess	1 (3)
Chest wall abscess	1 (3)
Disseminated miliary disease	1 (3)
Disease outcome	
Death attributed to *M. tuberculosis*[b]	7 (23)
Received anti-mycobacterial combination therapy	29 (97)
Responded to therapy[c]	23 (79)
Deaths attributed to *M. tuberculosis* in treated group	6 (21)

[a]Five patients with upper-lobe disease had concomitant pleural effusion.
[b]Deaths were attributed to *M. tuberculosis* if there was autopsy-proven tuberculous organ disease or severe damage to organs.
[c]Anti-mycobacterial agents were not given to one patient whose death was attributed to *M. tuberculosis*.

Table 2 shows the disease characteristics in the 30 patients. Five of 19 patients with lung disease had concurrent pleural effusion, and tuberculous pleurisy was present in three (10%) patients. Acid-fast bacilli were identified in 35% of bronchoalveolar lavage samples on cytological examination, whereas all except one bronchoalveolar lavage culture sample (95%) in patients with pulmonary tuberculosis were diagnostic. Four patients had received haematopoeitic stem cell transplants; three of these had isolated pulmonary disease, and one presented with tuberculous lymphadenitis. The interval from transplant to diagnosis of tuberculosis ranged from 2 to 379 days.

Twenty-nine (97%) patients had received appropriate antimicrobial therapy. Seven (23%) patients died; anti-tuberculosis therapy was not commenced in one of these patients, and the correct diagnosis was delayed in five patients. Despite appropriate antimicrobial therapy, all four patients who received high-dose corticosteroids died, compared to only two deaths in 25 patients with no history of corticosteroid use ($p < 0.001$; OR 8.67). All 28 isolates of *M. tuberculosis* were susceptible to first-line anti-tuberculosis agents.

Active tuberculosis was uncommon in the cancer patients studied, and was seen mostly in patients born in countries outside the USA. In these individuals, in contrast to persons born in the USA, tuberculosis probably represented reactivation of latent infection [11, 12]. It was interesting to note that most patients did not receive systemic corticosteroids, and that severe protein–calorie malnutrition was conspicuously absent in this group. The high mortality rate (100%) observed in patients receiving high-dose systemic corticosteroids, compared with those who did not, suggests prompt discontinuation of corticosteroids in cancer patients with active tuberculosis. However, the low rate of infection-related deaths (< 10%) in cancer patients without recent significant corticosteroid exposure was encouraging.

A high proportion of patients had a haematological malignancy, especially leukaemia, with active tuberculosis. This was in contrast to previous reports indicating a higher rate of tuberculosis in patients with solid-organ malignancy and Hodgkin's disease [3]. Active tuberculosis was an uncommon opportunistic complication in the stem cell transplant recipients, and all four patients in this group presented with localised, non-disseminated disease that responded to therapy.

The emergence and global spread of MDR *M. tuberculosis* is a serious concern, as these infections are refractory to conventional therapy [7], and successful treatment often involves a multi-faceted approach [8, 13]. In the present report, all clinical isolates of *M. tuberculosis* from cancer patients were susceptible to first-line antimicrobial agents. Ineffective person-to-person transmission of MDR *M. tuberculosis* [14] may be responsible, in part, for the absence of drug-resistant infection in the cancer patients studied. Alternatively, most active tuberculosis in immigrants probably involved reactivation of a drug-susceptible mycobacterial infection acquired remotely. The paucity of MDR mycobacteriosis may have played an important role in promoting a favourable treatment outcome in the patients without corticosteroid exposure [14,15].

Tuberculosis can imitate the clinical and radiographic features of various diseases; abdomino-pelvic infections may occasionally be misinterpreted as cancer [16,17]. In this report, nearly 60% of patients with focal pulmonary tuberculosis were thought initially to have cancer. Importantly, tuberculosis can coexist with cancer [18,19], and a high level of suspicion is crucial in this select group of patients. In accordance with the results of this study, others have reported higher bronchoscopic diagnostic yields compared to sputum cultures [20]. For patients with a high pre-test probability of coexisting tuberculosis and cancer, trans-thoracic fine needle aspiration or evaluation of surgically obtained lung tissue may facilitate a timely diagnosis [21].

In conclusion, tuberculosis was rare in the cancer patients and stem cell transplant recipients studied. Infection was most prominent in immigrants, and leukaemia was observed to be an important underlying malignancy. The paucity of conventional predictors of tuberculosis, such as lymphocytopenia, severe malnutrition and systemic corticosteroids, was unexpected. A favourable treatment response can be expected in cancer patients with active tuberculosis who have not recently undergone high-dose systemic corticosteroid therapy.

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RESEARCH NOTE

Extended-spectrum β-lactamase (ESBL) CTX-M-15-producing *Escherichia coli* and *Klebsiella pneumoniae* in Sofia, Bulgaria

R. Markovska[1], *I. Schneider*[2], *E. Keuleyan*[3] *and A. Bauernfeind*[2]

[1]Department of Microbiology, Medical University, Ministry of the Interior, Sofia, Bulgaria, [2]MICOER Institute, Munich, Germany and [3]Medical Institute, Ministry of the Interior, Sofia, Bulgaria

ABSTRACT

During a survey of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae in Bulgaria in 2001–2002, three isolates from Sofia (two *Escherichia coli*, one *Klebsiella pneumoniae*) showed cefotaxime MICs that were decreased in the presence of clavulanate and were 2–8-fold higher than those of ceftazidime. Resistance was transferred to a sensitive recipient strain of *E. coli*. Both wild-type and transconjugant strains produced a cefotaxime-hydrolysing β-lactamase of pI 8.8. Sequencing of the PCR product obtained with oligonucleotide primers binding outside the coding region identified this β-lactamase as CTX-M-15. To our knowledge, this is the first report of CTX-M-15 in Bulgaria.

Corresponding author and reprint requests: R. Markovska, Department of Microbiology, Medical University, 2 Zdrave Str., 1431 Sofia, Bulgaria
E-mail: markovska73@abv.bg

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CTX-M-type β-lactamases are a group of class A extended-spectrum β-lactamases (ESBLs) that are growing rapidly in importance [1,2]. CTX-M-1, the first CTX-M-type β-lactamase, was detected in an isolate of *Escherichia coli* from Germany in 1989 [2], and the overall number of cefotaximases has now increased to *c*. 40 [3]. Most CTX-M-type β-lactamases are 4–16-fold more active against cefotaxime than against ceftazidime [1,4], but enzymes with enhanced activity against ceftazidime have been detected recently, namely CTX-M-15, -16, -19 and -27 [4–8]. CTX-M-15 was first described in India in 2001 [5], and was then identified subsequently in Poland, France, Turkey, Romania and the UK [4,9–12].

During a prospective survey of ESBLs in Enterobacteriaceae from seven Bulgarian university hospitals in 2001–2002, 62 ESBL-producing isolates were detected. Of these, three strains from Sofia were identified (see below) as CTX-M-15 producers: *E. coli* Sof_{10} was isolated on 9 February 2001 from the urine of a female ambulatory patient aged 60 years; *Klebsiella pneumoniae* Sof_9 was isolated on 18 April 2002 from the blood culture of a male patient, aged 47 years, in an intensive care unit; and *E. coli* Sof_{11} was recovered on 21 February 2002 from the blood culture of a boy, aged 10 months, with pyelonephritis.

Antimicrobial susceptibilities were determined by disk diffusion and an agar dilution procedure, performed according to National Committee for Clinical Laboratory Standards guidelines [13]. Plasmid transfer was performed on Mueller–Hinton agar by mixing 0.8-mL portions of 18–24-h Luria–Bertani broth cultures of the donor and recipient (*E. coli* K_{12}:W_{3110} Rif^r lac^-) strains. Transconjugants were selected on MacConkey agar containing cefotaxime 2 mg/L and rifampicin 50 mg/L. Analytical isoelectric focusing was done according to the method of Mathew *et al.* [14] with modifications [2]. A bioassay was used to determine the hydrolytic activity of the distinct β-lactamase bands after isoelectric focusing as